Nevirapine and its impact on the lipid profiles of HIV-infected patients

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Abstract
The focus of several studies has been the relationship between antiretroviral therapy and cardiovascular disease, in particular the outcome of atherosclerosis in HIV-infected patients with low HDL-c levels. HIV-disease itself results in changes in the lipid metabolism. Reduced HDL-c in untreated HIV-infection is partially corrected after the initiation of ART, but long-term treatment may lower HDL-c again and in addition raise other cholesterol fractions even further.

It has however been established that NNRTIs, such as nevirapine and efavirenz, increase HDL-c levels potently. Nevirapine has been documented to increase HDL-c and improve TC/HDL-c ratio more so than does efavirenz. The less atherogenic lipid profile of nevirapine may make it a suitable component in first-line regimens for HIV-positive patients with multiple risk factors of CHD, such as low HDL-c.

In second-line regimens nevirapine has also been found effective. In treatment-experienced patients, the PI component could be substituted for nevirapine in order to simplify treatment and to improve PI-initiated lipid abnormalities, but correction of all the cholesterol fractions may not be accomplished.

Introduction
Morbidity and mortality related to human immunodeficiency virus type 1 (HIV-1) infection have been remarkably reduced with combination antiretroviral therapy (ART).

(DAD) study signified a 26% enhanced prevalence of myocardial infarction per additional year of exposure to combination antiretroviral therapy. In a three year follow-up report, which assessed the risk of myocardial infarction associated with Protease Inhibitors (PIs) and Nonnucleoside Reverse-Transcriptase Inhibitors (NNRTIs), a significant correlation was found for PIs, but not for NNRTIs. The PIs are known to cause metabolic changes, lipodystrophy and increase in blood lipids. Hyperlipidaemia is a recognised risk factor for cardiovascular disease. On the other hand, high-density lipoprotein cholesterol (HDL-c) is a powerful autonomous epidemiologic factor associated with reduced cardiovascular disease. On the other hand, high-density lipoprotein cholesterol (HDL-c) is a powerful autonomous epidemiologic factor associated with reduced cardiovascular disease (CVD) risk by mechanism of restraining oxidation and inflammation and increasing cholesterol efflux.

It has been documented that NNRTIs, such as nevirapine and efavirenz, increase HDL-c levels. The HDL-c raise encouraged with NNRTI-containing ART surpasses increases achieved with any of the existing statins or fibrates. Nevirapine, in particular, has been associated with a marked increase in HDL-c. This may be of importance in selecting appropriate regimens for first line treatment, as well as simplified, effective therapy in treatment-experienced HIV patients.

Lipid changes due to HIV-infection
The HIV-disease itself is associated with transformed lipid metabolism. Please refer to Figure 1.

Figure 1: Hypothesis of the effects of the HIV-infection on cellular cholesterol metabolism

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Lipid profiles of HIV-infected patients before the era of Highly Active Antiretroviral Therapy (HAART)

- ↓ Serum apoA-I availability → ↓ HDL-c construction \(^\text{12}\)
- ↓ TG clearance + ↑ assemblage of hepatic very low-density lipoprotein (VLDL) → ↑ circulating triglyceride (TG) levels → Hypertriglyceridaemia \(^\text{c}\) \(^\text{16}\)
- ↓ Low-density lipoprotein (LDL) and total cholesterol (TC) \(^\text{14}\) \(^\text{16}\)

Lipid profiles after commencement of HAART

- TC and LDL-c ↑ to preinfection levels \(^\text{16}\)
- ↑ in HDL-c, which may symbolise a ‘return to health’, but not to pre-infection levels, thus resulting in net ↓ HDL \(^\text{12}\) \(^\text{16}\) \(^\text{17}\)
- ↑ lipolysis → ↑ plasma free fatty acids (FFA) \(^\text{12}\)
- Incomplete oxidative clearance of released FFA → ↑ TG + VLDL construction \(^\text{12}\)

Amplified cardiovascular risk in the HIV-positive population may also be attributed to endothelial malfunction, weakened fibrinolysis and inflammation overload. C-reactive protein (CRP), tissue plasminogen activator (tPA), plasminogen activator-1 (PAI-1) and homocysteine concentrations are all increased and show a relationship with the threat of myocardial infarction in HIV-positive patients.\(^4\)

When to commence antiretroviral treatment (ART) and which regimen?

The US and Europe HIV treatment guidelines advocate that ART should be initiated when a patient’s CD4 cell count descends beneath 350 cells/mm\(^3\).\(^18\) Furthermore, in February 2008, data presented to CROI (Conference on Retroviruses and Opportunistic Infections) confirmed that untreated HIV-positive patients had an increased risk of death in comparison with the common population, even when CD4 cell counts in the infected patients were greater than 350 cells/mm\(^3\).\(^18\)

However, according to the latest World Health Organization (WHO) guidelines (2007), the most favourable time to commence ART in patients with a CD4 cell count of 200-350 cell/mm\(^3\) is still unidentified.\(^19\)

Considering that long-term exposure to combination antiretroviral therapy causes dyslipidaemia and increases the risk of myocardial infarction, the current debate around the ideal time to initiate antiretroviral treatment is understandable.\(^18\)

Therefore, when HAART is started, an essential factor in choosing the most advantageous first-line regimen is the probable long-standing metabolic outcomes of antiretroviral (ARV) medications.\(^12\)

The WHO-recommended first- and second-line antiretroviral regimens are shown in Table 1.

Choice between NNRTIs and the changes they exert on lipid profiles

All the classes of ARVs, namely PIs, Nucleoside Reverse-Transcriptase Inhibitors (NRTIs) and NNRTIs are correlated with dyslipidaemia.\(^19\) Elevated levels of TGs, TC and LDL are frequently related to PI-based regimens. On the contrary, NNRTI-based regimens show smaller increases in LDL-c and TGs and discernible increases in HDL-c.\(^11\)

The 2NN Study

This multicentre, open-label, randomised study compared the NNRTIs nevirapine and efavirenz. 1216 patients from 65 different study locations in Asia, North and South America, Australia, South Africa and Europe were included.\(^11\)\(^20\)

Patients registered were 16 years of age or older, ART-naïve and had a plasma HIV-1 RNA concentration (pVL) of ≥5000 copies/ml. All patients received d4T twice daily (bd) and 3TC bd in conjunction with randomly allocated NVP 400mg once daily (od)/ 200mg bd, EFV 600mg od, or NVP 400mg + EFV 800 mg od combined for 48 weeks.\(^11\)\(^20\)

The study concluded that:

- Triple drug regimens with either NNRTI illustrated no significant distinction in treatment failure in ART-naïve HIV-1-infected patients and that either NNRTI is suitable as part of first line treatment.
- Simultaneous use of NVP and EFV is not advocated, due to toxicity in the absence of augmented virologic efficacy.

A prospective subanalysis of the 2NN study

A prospective, preplanned, on-treatment analysis of lipids and lipoprotein changes in the NVP and EFV treatment groups of the 2NN study was executed. Only patients who used all components of their assigned treatment no less than 95% of the time during the 48-week follow-up were included. The NVP-od and NVP-bd groups were combined resulting in a final sample size of 417 patients in the NVP group and 289 in the EFV group.\(^11\)

Plasma samples at baseline, as well as weeks 2, 4, 8, 12, 24, 36 and 48 were obtained for the potential determination of lipids and lipoproteins. Blood was drawn after a compulsory fast of at least 3 hours.\(^11\)

<table>
<thead>
<tr>
<th>Table 1: WHO-recommended first- and second-line ARV regimens(^18)</th>
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</thead>
<tbody>
<tr>
<td><strong>First-line regimen</strong></td>
</tr>
<tr>
<td>Reverse-Transcriptase Inhibitor (RTI) + Protease Inhibitor (PI)</td>
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<tr>
<td><strong>Preferred</strong></td>
</tr>
<tr>
<td>AZT + 3TC + NVP</td>
</tr>
<tr>
<td>AZT + 3TC + EFV</td>
</tr>
<tr>
<td>d4T + 3TC + NVP/EFV</td>
</tr>
<tr>
<td><strong>Alternative</strong></td>
</tr>
<tr>
<td>AZT/d4T + 3TC + TDF/ABC</td>
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The primary study outcome was the mean % change in various lipid fractions between start of assigned treatment and week 48:11
- HDL-c
- TC
- TC:HDL-c ratio
- Non-HDL-c
- LDL-c
- TGs

The results of the lipid assessment are given in Table 2.

Discussion

Part of the alterations in lipids may perhaps reveal a ‘return to normal’ due to treatment. Generally a larger increase in all lipid concentrations, except TGs, correlated with larger decreases in pVL. However, the extent of the HDL-c increase in patients experiencing virologic failure in comparison to those with complete viral suppression during the 48 week analysis varied insignificantly. After adjustment for alterations in HIV-1 RNA and CD4 cell levels due to treatment, above distinctions between NVP and EFV remained, representing an additional outcome of the drugs on lipids other than sufficient suppression of HIV-1 infection.11

Several studies substantiate that a significant decline in CHD mortality, independent of changes in LDL-c, correlates with an increase in HDL-c. Theoretical estimates of these studies, taking the observed effects on both HDL-c and LDL-c into account, indicate a reduction of 15% in CHD risk for patients taking NVP than for patients taking EFV.11

The less atherogenic lipid profile of nevirapine in comparison to efavirenz may be an important factor when considering first-line regimens for HIV-positive people with multiple risk factors of CHD. In a patient population using not only ART, but also a substantial amount of affiliated medication, the added introduction of lipid-lowering agents, which may cause drug-drug interactions, could influence treatment adherence, which is fundamental for continued success of ARV treatment.11

Hypothesis of the mechanisms by which nevirapine influences HDL

Earlier studies concluded that nevirapine prospectively stimulates synthesis of ApoA-I, as seen with increases in ApoA-I, lipoprotein(a) and HDL particle size.12 ApoA-I is the defining protein constituent of HDL and its structure modulates HDL size, shape and function.12 The interaction of lipid-free ApoA-I with ABCA1 promotes cholesterol efflux from macrophages, a key reaction for the formation of HDL particles and maintenance of HDL levels.15,21

The Nevirapine Intensive Lipid Evaluation (NILE) trial also confirmed that nevirapine increases HDL particle size and raises HDL-c levels by endorsing ApoA-I production. Clearance of HDL particles was however not likely to be decreased, as the enzyme Cholesterol Ester Transfer Protein (CETP) involved in HDL metabolism, was not inhibited by NVP.8,17 Other enzymes involved in the synthesis and degrading of HDL were also not changed.17

In the ILLUMINATE trial, patients treated with torcetrapib (a CETP inhibitor), exposed a statistically significant surplus of deaths and cardiovascular events associated with the drug. One possible explanation for this negative result, despite increased HDL levels, is that the HDL particles produced by CETP inhibition may be dysfunctional.5 Subsequently it was stated by Reilly and Tall that HDL function, and benefit of a particular drug, may depend more on the molecular mechanism facilitating the HDL increase and/or HDL subfractions than on the absolute level of HDL-c.10

In view of the results from the follow-up to the DAD study and findings from ILLUMINATE and NILE, nevirapine therefore seems to increase HDL in a way that provides safeguard against CV disease.1,8,9

Nevirapine as replacement for PI

Simplified HAART regimens are becoming extensively used, predominantly as a consequence of the extensive range of side-effects, drug interactions and food or drink limitations associated with PI-based regimens. The PIs are known to cause metabolic irregularities such as diabetes mellitus, hypertriglyceridaemia and hypercholesterolaemia, resulting in an amplified risk of cardiovascular disease.2,3

Paloma Gil et al assessed the long-term efficacy and safety of Protease Inhibitor

| Table 2: Changes in lipids from baseline to 48 weeks in the 2NN sub-study11 |
|----------------|----------------|----------------|----------------|----------------|
| Patients taking NVP | Patients taking EFV | Difference NVP – EFV | P-Value for difference |
| % HDL increase | 42.5% | 33.7% | 8.9% | p = 0.036 |
| % TC increase | 26.9% | 31.1% | -4.2% | p = 0.073 (NS) |
| % TC:HDL-c ratio change | -4.1% | +5.9% | -10% | p < 0.001 |
| % Non-HDL-c increase | 24.7% | 33.6% | -8.9% | p = 0.007 |
| % TG increase | 20.1% | 49.0% | -28.9% | p < 0.001 |
| % LDL increase | 35.4% | 40.0% | -4.6% | p = 0.378 (NS) |

NS = not significant

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switching to nevirapine in HIV-infected patients with undetectable viral load.

This was a prospective, observational, longitudinal study of 110 patients receiving HAART, consisting of 2 NRTIs (didanosine, lamivudine, stavudine or zidovudine) and a PI (indinavir, nelfinavir, ritonavir or saquinavir). At the commencement of HAART, 79 patients were treatment naïve and 31 patients were previously treated with mono- or double therapy.²

Criteria for patients included
• Virus load < 200 copies/ml for ≥ 3 months before termination of PI therapy
• A reason for discontinuing the PI²

Aims of the Study
• To assess the long-term (3-year) effectiveness of the combination of 2 NRTIs plus NVP in sustaining viral load and CD4 lymphocyte counts after exchange from a PI-based regimen.
• Evaluation of the short- and long-term progress of biochemical irregularities, such as increased creatinine, cholesterol and triglyceride serum levels, related to PI use after withholding treatment.
• Assessment of tolerance and side-effects after long-term use of the new regimen.²

Results
Main reason for PI switching:²
• Voluntary treatment simplification – 49 patients
• Lipodystrophy (redistribution of peripheral fat) – 26 patients
• Renal dysfunction and/or nephrolithiasis associated with IDV – 25 patients
• Isolated hypertriglyceridaemia – 6 patients
• Hypercholesterolaemia – 6 patients

The results of immunological and virological assessments are given in Table 3.

The results of metabolic measurements are given in Table 4.

Nevirapine treatment was discontinued in 33 patients due to the following:²
• NVP-associated side-effects – 16 patients:
  - Acute icteric hepatitis – 2 patients
  - Significant ↑ transaminase levels – 5 patients
  - Hepatotoxicity – 6 patients
  - Skin rash – 7 patients
  - Acute methadone-withdrawal syndrome – 2 patients
• Voluntary treatment interruption – 3 patients
• Change to another simplified HAART regimen – 3 patients
• Coexisting acute viral hepatitis A – 2 patients
• Rebound in virus load – 9 patients

Discussion
96% of the patients sustained an intraceable viral load. An increase in CD4 T cells was also seen. In the 31 patients who were not treatment naïve at initiation of the PI-based regimen, treatment failure was not universally detected after switching to nevirapine. Unfavourable clinical incidents correlating with progres-

Table 3: Immunological and virological outcomes after discontinuation of PI therapy and initiation of Nevirapine therapy²

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Mean CD4 cell count (cells/µl)</th>
<th>Mean increase (cells/µl) in remaining patients</th>
<th>P-value for difference</th>
<th>Number of patients with undetectable virus load maintained in intention-to-treat analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Value</td>
<td>110</td>
<td>628 ± 32.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First year</td>
<td>88</td>
<td>684.9 ± 34.5</td>
<td>57</td>
<td>83 (75.5%) of 110</td>
</tr>
<tr>
<td>Second year</td>
<td>77</td>
<td>716.8 ± 39.3</td>
<td>84</td>
<td>77 (70%) of 110</td>
</tr>
<tr>
<td>Third year</td>
<td>68</td>
<td>745.5 ± 43.9</td>
<td>90</td>
<td>68 (61.8%) of 110</td>
</tr>
</tbody>
</table>

NS = not significant

Table 4: Metabolic outcomes after discontinuation of PI therapy and initiation of Nevirapine therapy²

<table>
<thead>
<tr>
<th></th>
<th>Mean serum cholesterol levels &gt; 240mg/dl* in 21 of the 110 patients</th>
<th>% Reduction in mean serum cholesterol from baseline</th>
<th>Mean serum triglyceride levels &gt; 400mg/dl** in 11 of the 110 patients</th>
<th>% Reduction in mean serum triglycerides from baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Value</td>
<td>296 ± 19.7</td>
<td>24.2%</td>
<td>1792.5 ± 580.7</td>
<td>74.8%</td>
</tr>
<tr>
<td>First year</td>
<td>224.3 ± 10.1</td>
<td>24.2%</td>
<td>452.1 ± 98.7</td>
<td>74.8%</td>
</tr>
<tr>
<td>Second year</td>
<td>228.12 ± 12.8</td>
<td>22.9%</td>
<td>421.8 ± 82</td>
<td>76.5%</td>
</tr>
<tr>
<td>Third year</td>
<td>232.2 ± 10.8</td>
<td>21.6%</td>
<td>460.8 ± 168.1</td>
<td>74.3%</td>
</tr>
<tr>
<td>P-value for change</td>
<td>p&lt;0.015</td>
<td></td>
<td>p &lt; 0.04</td>
<td></td>
</tr>
</tbody>
</table>

*240 mg/dl = 6.20 mmol/L
**400 mg/dl = 4.52 mmol/L
sion to AIDS were not experienced by patients, which propose that switching to nevirapine for sustained long-term immunological and virological control in HIV-infected patients may be safely advocated.

In the short- and long-term follow-up of the study there was a striking decrease in serum triglyceride levels. The main decrease was seen after 2 years with a slight increase again after 3 years on nevirapine. After the switch to the nevirapine regimen a significant decrease in total cholesterol levels was observed for years 1, 2 and 3. However, after year 1 a mild increase in serum cholesterol levels was observed in the following months. Unfortunately no information regarding high- and low density lipoprotein levels were gathered.

In a subset of the similar NEFAs study metabolic benefits were assessed 24 months after treatment simplification by replacing a protease inhibitor with abacavir, efavirenz or nevirapine. The results showed significant increases in HDL-c in both NNRTI-containing regimens at 12 (EFV, 17%; NVP, 21%) and 24 months (EFV, 15%; NVP, 21%). These alterations resulted in a significant reduction in the median TC/HDL-c ratios at 12 (EFV, 16%; NVP, 19%) and 24 months (EFV, 14%; NVP, 19%), with a trend in favour of NVP. Meaningful decreases in the non-HDL-c fraction as well as triglycerides levels were observed at the 12 month assessment in all three arms. TG levels increased again, all through the second year, but did not surpass primary values.

The TC/HDL-c ratio is concluded by numerous observational studies to be the main single variable in forecasting cardiovascular events and NNRTI-based regimens may therefore be cardioprotective.

Conclusion

The focus of several studies has been the affiliation between ART and CVD. Much emphasis has been placed on the outcome of atherosclerosis in HIV-infected patients in correlation with low HDL-c levels. Reduced HDL-c in untreated HIV-infection is partially corrected after the commencement of ART, but long-standing treatment may lower HDL-c again and in addition raises VLDL and LDL levels. The pathophysiological mechanism of dyslipidaemia seen in HIV-infected patients and the effects of various HAART regimens need to be clarified with further studies.

Nevirapine increases HDL-c and improves TC/HDL-c ratio, apparently more so than does efavirenz. Less atherogenic lipid profile of nevirapine may make it a suitable component in first-line regimens for HIV-positive patients with multiple risk factors of CHD, one of which include low HDL-c. In second-line regimens the PI component could be substituted for nevirapine in order to improve PI-initiated lipid abnormalities, but normalisation of all the cholesterol fractions may not be achieved.

However, the choice between nevirapine and efavirenz will also depend on the patient’s clinical profile and contra-indications to the use of either drug.

Ultimately the threat of progression of HIV disease must be balanced against the possible development of cardiovascular disease with long-term combination ARV-therapy. CVD risk should be reduced by standard dietary and lifestyle modifications, including interventions for hypertension, smoking and dyslipidaemia, but clinicians should also consider efficient antiretroviral agents which are least inclined to increase glucose or lipid levels.

References: